Living-donor lobar lung transplantation for various lung diseases

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Objective: We report on our early experience in living-donor lobar lung transplantation for patients with various lung diseases including restrictive, obstructive, septic, and hypertensive lung diseases.

Methods: From October 1998 to March 2002, living-donor lobar lung transplantation was performed in 14 patients with end-stage lung diseases. There were 11 female patients and 3 male patients, with ages ranging from 8 to 53 years, including 4 children and 10 adults. Diagnoses included primary pulmonary hypertension (n = 6), idiopathic interstitial pneumonia (n = 2), bronchiolitis obliterans (n = 2), bronchiectasis (n = 2), lymphangioleiomyomatosis (n = 1), and cystic fibrosis (n = 1). Bilateral living-donor lobar lung transplantation was performed in 13 patients and right single living-donor lobar lung transplantation was performed for a 10-year-old boy with primary pulmonary hypertension.

Results: All the 14 patients are currently alive with a follow-up period of 4 to 45 months. Although their forced vital capacity (1327 ± 78 mL, 50.2% of predicted) was limited at discharge, arterial oxygen tension on room air (98.5 ± 1.8 mm Hg) and systolic pulmonary artery pressure (24.8 ± 1.6 mm Hg) were excellent. Forced vital capacity improved gradually and reached 1894 ± 99 mL, 67.4% of predicted, at 1 year. All donors have returned to their previous lifestyles.

Conclusions: Living-donor lobar lung transplantation can be applied to restrictive, obstructive, septic, and hypertensive lung diseases. This type of procedure can be an alternative to conventional cadaveric lung transplantation for both pediatric and adult patients who would die soon otherwise.

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Living-donor lobar lung transplantation (LDLLT) was developed by Dr Starnes and his colleagues with satisfactory intermediate survival and functional results.[1] Their excellent works encouraged us to apply the operation to critically ill patients with a wide rage of pathophysiology at Okayama University Hospital in Japan. We report on our early experience with our first 14 patients receiving LDLLT.

Methods

Patient and Donor Selection

Patients being considered for LDLLT should meet the criteria for conventional bilateral lung transplantation. The policy of our program has been to limit LDLLT to critically ill patients who are unlikely to survive the long wait for cadaveric lungs. Inclusion criteria for donor were as follows:

Relatives within the second degree or a spouse
20 ≤ age ≤ 55 years
ABO compatibility
No significant medical history or active medical problems
No recent viral infection
No abnormalities on the echocardiogram
No significant pulmonary pathology on computed tomography on donor side

Arterial oxygen tension > 80 mm Hg
Forced vital capacity, forced expiratory volume in 1 second > 85% of predicted
No previous thoracic operation on donor side

Potential donors were interviewed by 3 physicians with an observer to safeguard against coercion and to ensure donor comprehension of the procedure. The interview was performed at least 3 times to provide potential donors multiple opportunities to question, reconsider, or withdraw as a donor. The larger donor was selected for donation of the right lower lobe.

After multidisciplinary assessment, each case was carefully discussed by the Lung Transplant Evaluation Committee at Okayama University Hospital. The members of the committee consisted of 3 pulmonologists, 3 surgeons, and 1 cardiologist.

Size Matching

Given that the right lower lobe consists of 5 segments, the left lower lobe of 4, and the whole lung of 19, total forced vital capacity (FVC) of the 2 grafts was estimated by the following equation.

$$\text{Total FVC of the 2 grafts} = \text{Measured FVC of the right donor} \times 5/19 + \text{Measured FVC of the left donor} \times 4/19$$

When the total FVC of the 2 grafts was >50% of the predicted FVC of the recipient (calculated from a knowledge of height, age, and sex), we accepted the size disparity regardless of the recipient's diagnosis.

Donor Technique

Epidural catheters for postoperative analgesia were placed routinely the day before the surgery to avoid complications related to heparinization during the donor lobectomies. The recipient and the right-side donor were brought to the separate operating rooms at the same time. The left-side donor was brought to the third operating room 30 minutes later. Three surgical teams were required and they communicated closely to minimize graft ischemic time. After induction of general anesthesia, donors were intubated with a left-sided double lumen endotracheal tube. Fiberoptic bronchoscopy was performed to determine if lower lobectomy was feasible, leaving adequate length for closure on the donor bronchus and length for anastomosis in the recipient.

A detailed description of the technical aspects of the donor lobectomy has been previously published by Starnes' group.[2] Briefly, the donors were placed in the lateral decubitus position, and a posterolateral thoracotomy was performed through the fifth intercostal space. Fissures were developed using linear stapling devices. The pericardium surrounding the inferior pulmonary vein was opened circumferentially. Dissection in the fissure was carried out to isolate the pulmonary artery to the lower lobe and to define the anatomy of the pulmonary arteries to the middle lobe in the right side of the donor and to the lingular segment in the left side of the donor. If the branches of the middle lobe artery and lingular artery were small, they were ligated and divided. Intravenous prostaglandin E1 was administered to decrease systolic blood pressure by 10 to 20 mm Hg. Ten thousand units of heparin and 500 mg of methylprednisolone were administered intravenously. After placing vascular clamps in appropriate positions, the division of the pulmonary vein, pulmonary artery, and bronchus were carried out in this order. Vascular stumps were oversewn with a 5-0 Prolene continuous suture (Ethicon, Tokyo, Japan). The bronchial stump was closed with 3-0 Prolene interrupted sutures. Then, each bronchial closure was covered with a pedicled pericardial fat tissue. Heparinization was reversed by administering protamine.

On the back table, the lobes were flushed with 1 L of Euro-Collins solution both antegradely and retrogradely from a bag about 50 cm above the table. Lobes were gently ventilated with room air during the flush.

Recipient Technique

Patients were anesthetized and intubated with a single lumen endotracheal tube in children and with a left-sided double lumen endotracheal tube in adults. A Swan-Ganz catheter was placed. Intraoperative transesophageal echocardiography was employed routinely. The "clamshell" incision was used and the sternum was transected. The ascending aorta and the right atrium were cannulated and patients were placed on standard cardiopulmonary bypass. After bilateral pneumonectomy, the right lower lobe implantation was performed followed by the left lower lobe implantation. The first implanted right graft was packed in iced saline and slush while the left graft was implanted. The sequence of the recipient anastomosis was the bronchus, vein, and artery. The bronchial anastomosis was begun with a running 4-0 polydioxanone suture for membranous portion and completed with simple interrupted sutures for cartilaginous portion. We used end-to-end anastomosis when the bronchial size was equivalent, and we used telescoping technique when the discrepancy in bronchial size was obvious. The bronchial wrapping was not employed except for the patients on high-dose steroid therapy. Just before completing the bilateral implantations, 500 mg to 1 g of methylprednisolone was given intravenously and nitric oxide inhalation was initiated at 20 ppm. After both lungs were reperfused and ventilated, cardiopulmonary bypass was removed. At the conclusion of the operation, a nasal feeding tube was inserted to the proximal jejunum under the fluoroscope.

Postoperative Management of the Recipient

The patient was kept intubated at a positive end-expiratory pressure of 5 cm H_2O for at least 3 days to maintain optimal expansion of the small lobes implanted. The suction of the chest drainage tubes started at 10 cm H_2O and gradually decreased to water seal in a couple of days. Fiberoptic bronchoscopy was performed every 12 hours while intubated to assess donor airway viability and to suction any retained secretions. An intensive program of chest physiotherapy was given every 4 hours and bedside postoperative pulmonary rehabilitation was initiated as soon as possible. Postoperative immunosuppression was a triple-drug therapy consisting of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and corticosteroids. Induction therapy with monoclonal or polyclonal antibodies has not been used. Acute rejection was clinically judged without transbronchial lung biopsy and treated with bolus injection of methylprednisolone. Cytomegalovirus prophylaxis with ganciclovir was given to all recipients for the first 3 months.

TABLE 1. Vital data of the 14 patients who underwent living-donor lobar lung transplantation

Case	Age, sex	Diagnosis	Height (cm)	Weight (kg)	BMI (kg/m^2)	Date of operation	O_2	Steroid	Epoprostenol	Inotropes	Ventilator	Emergency	Outcome
1	24, F	BE (PCD)	153	36.5	15.6	10/28/98	+			+	+	+	45 months, alive
2	29, F	BO (after BMT)	149	32.6	14.7	5/10/00	+	+					27 months, alive
3	23, F	LAM	148	36	16.4	10/18/00	+						21 months, alive
4	19, F	PPH	157	38	15.4	1/5/01	+		+	+			19 months, alive
5	38, F	IIP	155	55	22.9	2/28/01	+	+					17 months, alive
6	13, M	BO (after SJS)	157	32.3	13.1	3/27/01	+	+				+	16 months, alive
7	10, M	PPH	122	20.4	13.6	5/14/01	+		+	+			15 months, alive
8	53, F	IIP	159	44	17.4	7/8/01	+	+		+	NIPPV	+	13 months, alive
9	27, F	PPH	160	50.8	19.8	7/23/01	+	+	+	+	NIPPV	+	12 months, alive
10	52, F	BE	137	35	18.7	8/13/01	+						12 months, alive
11	8, M	PPH	126	20	12.6	11/19/01	+		+	+			8 months, alive
12	13, F	PPH	147	29.7	13.4	2/18/02	+		+	+			5 months, alive
13	25, F	CF	154	29	12.2	2/25/02	+	+			+	+	5 months, alive
14	31, F	PPH	160	41.7	16.3	3/25/02	+		+	+			4 months, alive

BE, Bronchiectasis; *PCD*, primary ciliary dyskinesia; *BO*, bronchiolitis obliterans; *BMT*, bone marrow transplantation; *LAM*, lymphangioleiomyomatosis; *PPH*, primary pulmonary hypertension; *IIP*, idiopathic interstitial pneumonia; *SJS*, Stevens-Johnson syndrome; *CF*, cystic fibrosis; *BMI*, body mass index; *NIPPV*, noninvasive positive pressure ventilator.

Results

Table 1 lists the preoperative data on the 14 patients who have undergone LDLLT from October 1998 through March 2002. There were 11 female patients and 3 male patients with ages ranging from 8 to 53 years (average 25.7 years). Four of the patients were children and 10 were adults. The height ranged from 122 cm to 160 cm (average 148.9 cm) and the weight ranged from 20 kg to 55 kg (average 35.8 kg). Body mass index (BMI) ranged from 12.2 kg/m^2 to 22.9 kg/m^2 (average 15.9 kg/m^2). Diagnoses included primary pulmonary hypertension (n = 6), idiopathic interstitial pneumonia (n = 2), bronchiolitis obliterans (n = 2, one after bone marrow transplant and one after Steven-Johnson syndrome[3]), bronchiectasis (n = 2, one associated with primary ciliary dyskinesia[4]), lymphangioleiomyomatosis (n = 1), and cystic fibrosis (n = 1). All patients were hospital-bound and were dependent on continuous oxygen inhalation. Six patients were steroid-dependent. All 6 patients with primary pulmonary hypertension (PPH) were on high-dose intravenous epoprostenol (average, 104.5 ng/kg/min) and inotropic therapy. Two patients (cases 1 and 13) were ventilator-dependent for 2 and 7 weeks, respectively. Two other patients were about to be intubated and required a noninvasive positive pressure ventilator with 100% inspired oxygen. Five patients received LDLLT on an emergency basis. Bilateral LDLLT was performed in 13 patients, and right single LDLLT was performed for a 10-year-old boy with PPH (case 7),[5] because his mother was the only available donor.

Among the 27 living-donors, 9 were the mothers of recipients, 6 were fathers, 5 were brothers, 3 were sisters, 2 were daughters, 1 was a son, and 1 was a husband. The average height and weight of the right-side donor were 168.0 cm and 66.4 kg, and those of the left-side donor were 159.0 cm and 55.8 kg, respectively. The total FVC of the 2 grafts was estimated to be ranging from 51.7% to 103.0% (average 67.0%) of the predicted FVC of the recipient.

Nine patients received an ABO-identical LDLLT and 5 patients (cases 2, 4, 10, 11, and 12) received LDLLT with a minor ABO mismatch.

In 6 patients (cases 1, 3, 4, 6, 8, and 9), partial cardiopulmonary bypass was initiated using the femoral vessels under local anesthesia because of their unstable preoperative condition. Then, they were anesthetized and intubated. Cardiopulmonary bypass was successfully removed from all 14 patients at the end of the procedure. The systolic pulmonary artery pressure was 38.9 ± 2.0 mm Hg immediately after the bypass was stopped. The ischemic time of the right graft was 154 ± 10 minutes, and that of the left graft was 99 ± 6 minutes.

The operative morbidity of the recipients is depicted in Table 2. Only 3 (21%) of 14 patients had no complications. The most frequent complication was lung edema, which occurred in 5 patients (36%). Tracheostomy was required in 6 patients, reintubation in 5, differential mechanical ventilation in 2, rethoracotomy in 2, and extracorporeal membrane oxygenation (ECMO) and continuous hemodiafiltration in 1. There were no airway complications in the 27 bronchial anastomoses. No infection was encountered. During the first month, acute rejection occurred at an average rate of 1.4 episodes/patient.

For the 14 recipients, duration of mechanical ventilation required was 9.5 ± 2.5 days, length of stay in the intensive care unit was 20.4 ± 3.6 days, and length of hospital stay was 57.3 ± 5.1 days. Functional assessment before discharge (1 to 3 months after transplantation) is summarized

TABLE 2. Operative complications in the 14 recipients

Complication	No. of patients
Lung edema	5 (36%)
Hemorrhage necessitating rethoracotomy	2 (14%)
Cardiac tamponade	2 (14%)
Left peroneal nerve palsy	2 (14%)
Renal failure	2 (14%)
Massive hemoptysis	1 (7%)
Hemolytic anemia	1 (7%)
Kinking of pulmonary artery	1 (7%)
Right phrenic nerve palsy	1 (7%)
Left recurrent nerve palsy	1 (7%)
Decubitus	1 (7%)

TABLE 3. Predischarge functional data of the 14 recipients (1 to 3 months)

	Mean ± SEM	Range
FVC (mL)	1327 ± 78	660-1810
%FVC (%)	50.2 ± 0.9	32.3-79.0
Pa_{O_2} (mm Hg)	98.5 ± 1.8	83.8-113.8
Systolic PAP (mm Hg)	24.8 ± 1.6	13-37
6-minute walk (m)	302 ± 19	140-390

FVC, Forced vital capacity; *Pa_{O_2},* arterial oxygen tension; *PAP,* pulmonary artery pressure; *SEM,* standard error of the mean.

in Table 3. Although the patients' FVC (1327 ± 78 mL, 50.2% of predicted) was limited at discharge, arterial oxygen tension on room air (98.5 ± 1.8 mm Hg) and systolic pulmonary artery pressure (24.8 ± 1.6 mm Hg) were excellent. FVC improved gradually and reached 1894 ± 99 mL, 67.4% of predicted, at 1 year (Figure 1). The patients' 6-minute walking distance also increased gradually during the first year (Figure 2). There was 1 recipient (7%) who developed bronchiolitis obliterans syndrome (BOS) 10 months after transplantation following cytomegalovirus infection (case 5). At the time of final data analysis in August 2002, the mean time from transplant to final analysis for the 14 patients was 15.6 months, ranging from 4 to 45 months. There has been no mortality during the observation period.

The operative morbidity of the donors is depicted in Table 4. Two donors developed middle lobe pneumonia associated with mild bronchial stricture. They were successfully treated with antibiotics and did not require bronchial dilatation. Atrial fibrillation, would infection, cholecystitis, and hemosputum were also conservatively treated with symptomatic improvement. One right-side donor required reconstruction of the middle lobe bronchus after the bronchus intermedius was inadvertently divided. One patient required rethoracotomy due to bleeding from chest wall; however, none of the patients required transfusion. All donors have returned to their previous lifestyles during the observation period.

Discussion

LDLLT is a new and evolving option for patients with end-stage lung disease. It was developed by Starnes' group[1] as an alternative to cadaveric lung transplantation. Because only 2 lobes are transplanted, this procedure seems to be best suited for children and small adults and has been applied most exclusively to cystic fibrosis. Recently, Starnes' group has expanded indications for LDLLT to include pediatric patients with PPH, bronchiolitis obliterans, and adult patients with pulmonary fibrosis.[6] Encouraged by Dr Starnes and his colleagues in California, we began to apply the procedure to a wider range of pathophysiology both for pediatric and adult patients.

Cystic fibrosis is a very rare disease in Japan. There were only 2 patients with cystic fibrosis among approximately 200 lung transplant referrals to Okayama University Hospital. Indications for lung transplant are quite distinct in Japan.[7] PPH, idiopathic interstitial pneumonia, and lymphangioleiomyomatosis (LAM) are the most frequent indications. The number of available cadaveric donors is quite limited (<5 cases/year in the whole country) and, furthermore, brain death is accepted only for those older than 15 years. Under the circumstance, it is clear that the only realistic option for most of our patients is to receive LDLLT.

The most frequent indication in this report was PPH (n = 6). Although most PPH patients who have sustained improvement of their condition with prostacyclin maintain this response,[8] sudden deterioration into life-threatening complications can occur. All 6 patients with PPH were on high-dose intravenous epoprostenol (average, 104.5 ng/kg/min) along with inotropic therapy. There were obvious concerns regarding whether pulmonary hypertension would develop in 2 lobes receiving a patient's entire cardiac output. Their systolic pulmonary artery pressure decreased from 91.7 ± 11.7 mm Hg to 28.3 ± 2.8 mm Hg at discharge, validating the functional capacity of the 2 lobes to handle the cardiac output of pediatric and adult recipients with PPH.[9] Of note was that right single lobe transplantation was successfully performed for a 10-year-old boy.[5] His mother's right lower lobe was estimated to be as big as his normal right lung. His systolic pulmonary artery pressure became 32 mm Hg even though the transplanted lobe received 77% of the cardiac output at 1 year.

The amount of tolerable size discrepancy between donors and recipients is currently unknown. The use of significantly undersized grafts is potentially problematic because it could result in poor ventilation due to remaining large dead space. We rely on the ratio between the total FVC of the 2 grafts to the predicted FVC of the recipient. When the ratio is greater than 0.5, we accept the size disparity regardless of the recipient's diagnosis. In fact, the LAM patient (case 3) had markedly hyperinflated lungs and

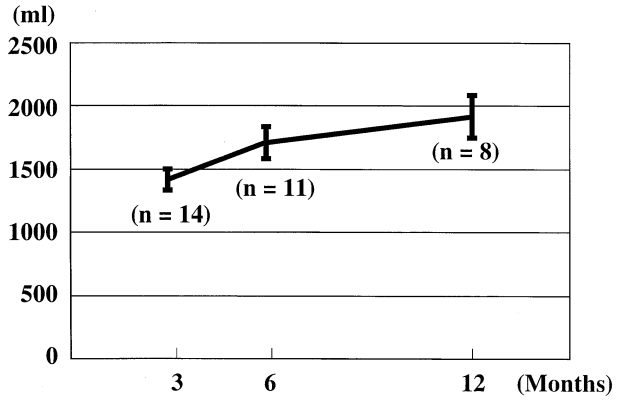

Figure 1. Change in forced vital capacity after living-donor lobar lung transplantation.

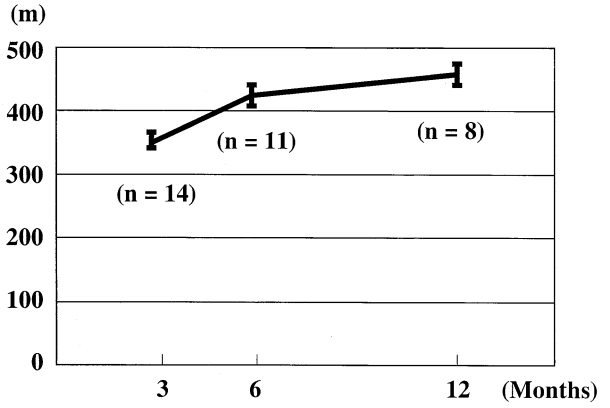

Figure 2. Change in 6-minute walking distance after living-donor lobar lung transplantation.

her lung was much larger than her donor's on chest x-ray. In case 5, the height of the left-side donor was 6 cm shorter than that of the recipient. However, none of our patients experienced any space problems after LDLLT.

All patients in this report had poor preoperative conditions and quite limited life expectancy. It has been well documented that PPH (n = 6), ventilator dependence (n = 2), and BMI < 17 (n = 10) are risk factors for operative mortality.[10,11] In most cases, patients far from our center were examined by the first author at the referral hospital. Five of them were transported on an emergency basis and underwent transplantation within as early as 40 hours of arrival.

Various operative complications occurred in 11 of 14 patients (79%), and some of them were unique to LDLLT. Lung edema was the most common complication, which occurred in 5 patients (36%). Knowing that the graft ischemic time was short in this procedure, the high incidence of lung edema must be related to the small grafts implanted. Of

TABLE 4. Operative complications in the 27 living-donors

Complication	No. of patients
Middle lobe pneumonia	2 (7%)
Atrial fibrilation	2 (7%)
Wound infection	2 (7%)
Sleeve lower lobectomy	1 (4%)
Hemorrhage necessitating rethoracotomy	1 (4%)
Cholecystitis	1 (4%)
Hemosputum	1 (4%)

note was that 3 PPH patients required reintubation due to lung edema associated with left ventricular failure on days 5 to 14, soon after they were extubated. This complication in patients with pulmonary hypertension has been also reported in bilateral lung transplantation.[12] Life-threatening massive hemoptysis was encountered in 1 patient (case 9), which was successfully treated with ECMO. Bronchoscopic examination demonstrated normal bronchial healing, and chest radiography revealed pulmonary hemorrhages in the right graft. Although the cause of the bleeding was unknown, it could be related to increased blood flow in the small grafts implanted. Transient hemolytic anemia occurred in 1 (case 2) of the 5 patients receiving LDLLT with a minor ABO mismatch. The patient was blood group A and received lobes from donors with blood group O. Donor-derived lymphocytes from blood group O lungs produced anti-A antibody and caused hemolytic anemia between 10 to 21 days after transplantation. She was successfully treated with transfusion of group O red cells without developing renal dysfunction.

In spite of poor preoperative condition and high incidence of operative complications, all recipients were sent home without need for oxygen inhalation. Because only 2 lobes were implanted, pulmonary function test demonstrated a limited FVC in recipients at discharge (50.2% of predicted FVC). However, repeated functional assessments demonstrated a steady improvement in FVC as well as in 6-minute walking distance during the first year as shown in the figures. To date, 13 of the 14 patients are active with no restrictions on activities of daily living. One patient with BOS (case 5) is still able to carry out daily activities but requires some restrictions. Her forced expiratory volume in 1 second decreased from 1650 mL at 6 months to 1110 mL at 1 year; thus she was diagnosed as BOS stage Ia. Her differential ventilation lung scan revealed marked air trapping to the right graft. Of note was that her right graft was the only one donated from a non–blood-related donor, her husband, among the 27 lobes in this report. Starnes and colleagues recently reported that pediatric patients receiving LDLLT had less BOS than those receiving conventional transplantation of cadaveric lungs, although the degree of

antigenic matches or mismatches do not explain these differences in BOS incidence.[13]

There has been a relatively low incidence of donor morbidity in our experience, and all donors have returned to their previous lifestyles during the observation period. However, serious complications, such as bronchial fistula and pulmonary embolism, have been reported.[14,15] Because of the possible serous morbidity associated with donor lobectomy, our policy has been to limit LDLLT to critically ill patients who are unable to wait for cadaveric lungs. We accept only relatives within the second degree or a spouse as living-donors, although other centers have expanded the donor indication to extended family members and unrelated individuals.[14,15]

Although our experience in LDLLT is still limited in numbers (n =14) and in observation period (4 to 45 months), the 100% successful rate is very encouraging. Meticulous perioperative management, including inhaled nitric oxide, frequent bronchoscopy, an intensive program of chest physiotherapy, and routine intubation for at least 3 days, is very important. We believe that "small but perfect graft" is a great advantage in this procedure. We conclude that LDLLT can be applied to various end-stage lung diseases including restrictive, obstructive, septic, and hypertensive lung diseases both for pediatric and adult patients.

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